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Hypertensive Response to Exercise: A Potential Cause for New Wall Motion Abnormality in the Absence of Coronary Artery Disease

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OBJECTIVES We sought to characterize patients with a hypertensive response during exercise echocardiography and its effect on results of the test.

BACKGROUND A hypertensive response to exercise has been shown to cause false-positive results in perfusion imaging, radionuclide angiography and exercise electrocardiography, but its influence on exercise echocardiography has not been reported.

METHODS We identified 548 of 6,686 patients who had coronary angiography within four weeks after exercise echocardiography from 1992 through 1996. Echocardiographic results from 132 patients (24%) with a hypertensive response to exercise, defined as systolic blood pressure (SBP) >220 mm Hg for men and SBP >190 mm Hg for women or as an increase in diastolic blood pressure (DBP) >10 mm Hg or DBP >90 mm Hg during exercise echocardiography, were compared with those from 416 patients without a hypertensive response.

RESULTS Of 132 patients with a hypertensive response to exercise, 108 patients had exercise echocardiographic results positive for ischemia. Of these patients, 24 (22%) were found to have no significant coronary artery disease (CAD). In contrast, of 320 patients with positive exercise echocardiographic results without a hypertensive response, 39 (12%) patients did not have significant CAD. Among the false-positive results, new wall motion abnormalities were extensive in 15 of 24 (63%) hypertensive responders involving >25% of segments compared with 14 of 39 nonhypertensive responders (36%, p = 0.012).

CONCLUSIONS An excessive rise in blood pressure during exercise is associated with a greater likelihood of new or worsening abnormalities with exercise, which may be observed in the absence of angiographically significant coronary artery stenosis. (J Am Coll Cardiol 2002;39:323–7)

Exercise echocardiography has emerged as a valuable technique for the noninvasive detection of coronary artery disease (CAD) (1–4). Although exercise echocardiography has been shown to be more accurate than exercise electrocardiography for the diagnosis of CAD (2,5,6), new regional wall motion abnormalities after exercise may occur in patients with normal coronary arteries. Because false-positive test results may lead to inappropriate clinical management, identification of factors contributing to false-positive results is clinically important.

Hypertension is often cited as a cause of false-positive exercise electrocardiographic results (7–10). Although hypertension has been reported to cause false-positive results with exercise electrocardiography and perfusion imaging (11–13), a similar observation has not been reported with exercise echocardiography. The purpose of this study was to characterize patients with a hypertensive response during exercise echocardiography and determine its effect on the results of the study.

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METHODS

From 6,686 consecutive patients who had first-time treadmill exercise echocardiography at our institution during a 15-year period, we identified 548 patients who had coronary angiography within four weeks after exercise echocardiography. Patients were classified into two groups, those with and those without a hypertensive response. A hypertensive response to exercise was defined as systolic blood pressure (SBP) >220 mm Hg for men and SBP >190 mm Hg for women (14) or as an increase in diastolic blood pressure (DBP) >10 mm Hg or DBP >90 mm Hg during exercise echocardiography (15).

Exercise echocardiography protocol. All patients participated in treadmill exercise testing. The Bruce protocol was used most frequently (90%), but modified Bruce and Naughton protocols were also used. Two-dimensional echocardiographic images at rest and immediately after exercise were obtained according to a standardized, previously published protocol (16). Digitized and videotape-recorded images were interpreted. Reviewers had no knowledge of clinical and exercise data. A normal exercise echocardiographic result was defined as a hyperdynamic response of all 16 left ventricular (LV) myocardial segments to exercise (17), ischemia as development of a new wall motion abnormality or worsening of resting hypokinesia and

Abbreviations and Acronyms

CAD = coronary artery disease
DBP = diastolic blood pressure
LV = left ventricular
SBP = systolic blood pressure

a fixed abnormality as a wall motion abnormality at rest that did not change after exercise (18). The percentage of ischemic segments was calculated as the ratio of the number of segments with new or worsening wall motion multiplied by 100 and divided by the total number of segments visualized. For determination of the number of coronary territories involved, the anteroseptal, anterior and apical segments were attributed to the left anterior descending coronary artery, the anterolateral and inferolateral segments to the left circumflex and the inferior and inferoseptal segments to the right coronary artery.

Coronary angiography. Coronary angiography was done at the discretion of the patient's cardiologist. Each angiogram was interpreted by two experienced angiographers who were unaware of the results of exercise echocardiography. Significant CAD was defined as narrowing of the luminal diameter of an epicardial vessel or major branch by ≥50%. Multivessel disease was defined by the presence of significant stenoses of two or more vessels.

Statistical analyses. Subjects were classified into groups on the basis of the presence or absence of a hypertensive response to exercise. Baseline clinical and exercise characteristics were compared using Student *t* test and Wilcoxon rank sum test for continuous variables and chi-square and Fisher exact tests for categorical variables. Sensitivity and specificity were conventionally defined by a comparison of echocardiography with angiography. Subjects were also classified into quartiles depending on SBPs and DBPs at peak exercise. The sensitivity and specificity according to blood pressure response of these groups were compared.

RESULTS

Population. Of 548 patients who had exercise echocardiography and coronary angiography, 376 were men and 172 were women, with a mean age of 67 ± 10 years. Of the patients, 132 (24%) had a hypertensive response to exercise. Table 1 describes the clinical characteristics of patients with and those without a hypertensive response. No significant differences were found for age, gender and history of hypertension, diabetes mellitus or LV hypertrophy. Patients with a hypertensive response were less likely to have a history of previous myocardial infarction and to be receiving beta-blocker therapy.

Table 2 describes the hemodynamic variables of both groups of patients. Patients with a hypertensive response had higher SBPs and DBPs at rest and a greater change in SBPs and DBPs with exercise. They also attained a higher peak exercise heart rate and rate-pressure product. However, there were no significant differences in exercise duration, metabolic equivalents and LV ejection fraction between the groups.

Table 1. Clinical Variables of Patients According to Blood Pressure Response to Exercise

	Hypertensive Response				
	Without (n = 416)		With (n = 132)		p Value
Age, yr ± SD	65 ± 10		66 ± 10		0.99
Men/women, no.	294/122		82/50		0.07
	No.	%	No.	%	
History of hypertension	218	52	78	59	0.27
Diabetes mellitus	67	16	12	9	0.22
Medications					
Beta-blockers	142	34	32	24	0.03
Digitalis	25	6	5	4	0.33
Calcium channel blockers	113	27	36	27	0.98
Previous MI	109	26	23	17	0.04

MI = myocardial infarction.

Exercise echocardiographic and angiographic findings. Overall, 73 patients had normal exercise echocardiographic results, 428 patients demonstrated ischemia and 47 patients showed a fixed wall motion abnormality. Two hundred sixty one patients had a resting wall motion abnormality. Of the patients, 107 (20%) had no significant coronary artery lesions at angiography, and 441 (80%) had significant CAD, including 102 (23%) with one-vessel disease, 115 (26%) with two-vessel disease and 224 (51%) with three-vessel disease. Exercise echocardiographic results were abnormal (ischemia or fixed wall motion abnormalities) in 363 of 441 patients with significant CAD (overall sensitivity, 82%). Of 107 patients without significant coronary artery stenosis, 42 had normal exercise echocardiographic results (overall specificity, 39%).

Table 2. Exercise and Echocardiographic Variables of Patients According to Blood Pressure Response to Exercise

	Hypertensive Response		
Variable	Without (n = 416)	With (n = 132)	p Value
Exercise duration, min ± SD	6.5 ± 2.4	6.8 ± 2.4	0.16
Metabolic equivalents	7.4 ± 2.3	7.6 ± 2.5	0.27
Blood pressure, mm Hg ± SD			
Baseline SBP	137 ± 21	146 ± 21	0.0001
Peak exercise SBP	161 ± 26	203 ± 23	<0.0001
Baseline DBP	82 ± 11	85 ± 10	0.0022
Peak exercise DBP	81 ± 11	100 ± 12	<0.0001
Change in SBP	24 ± 28	57 ± 24	<0.0001
Change in DBP	0 ± 12	15 ± 11	<0.0001
Heart rate, beats/min ± SD			
Baseline	72 ± 14	75 ± 13	0.028
Peak exercise	133 ± 23	145 ± 22	<0.0001
Double product	21,545 ± 5,685	29,343 ± 5,717	<0.0001
LV ejection fraction, %	53 ± 10	54 ± 9	0.89

DBP = diastolic blood pressure; LV = left ventricular; SBP = systolic blood pressure.

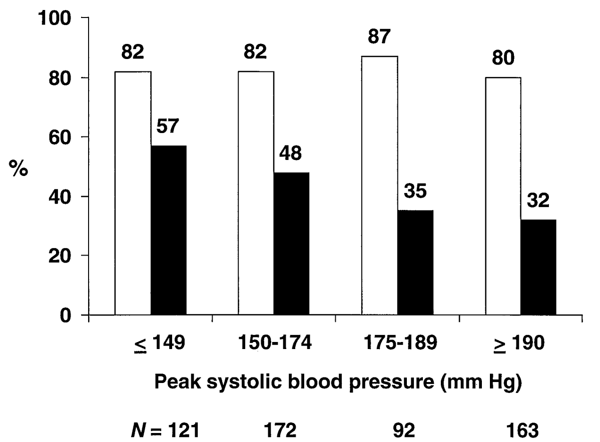

Figure 1. Sensitivity and specificity of exercise echocardiography according to peak systolic blood pressure response to exercise. **Open bar** = sensitivity; **solid bar** = specificity.

Relation of exercise echocardiographic results and blood pressure. Of 132 patients with a hypertensive response to exercise, 108 had exercise echocardiographic results positive for ischemia. Of the 108 patients, 24 (22%) were found to have no significant CAD. Conversely, of 416 patients without a hypertensive response to exercise, 320 had exercise echocardiographic results positive for ischemia, and 39 of the 320 (12%) were found to have no significant CAD. When the population was divided into quartiles on the basis of blood pressure at peak exercise, the specificity of exercise echocardiography decreased progressively as SBP increased with exercise ($p = 0.055$), whereas the sensitivity remained unchanged in all subgroups ($p = 0.85$) (Fig. 1); the same effect on specificity was observed as DBP increased with exercise ($p = 0.013$) (Fig. 2).

Among the studies with false-positive results, the percentage of ischemic segments was significantly greater in hypertensive responders (63%) than it was in nonhypertensive responders (36%) ($p = 0.012$). In addition, an ischemic wall motion abnormality in more than one coronary artery territory was more common in hypertensive responders (88%) than it was in nonhypertensive responders (69%), although this difference was not significant ($p = 0.098$). Figure 3 represents an exercise echocardiogram obtained from a patient with a hypertensive response to exercise and a normal coronary angiogram. The extensive wall motion abnormalities suggest left main or severe multivessel CAD.

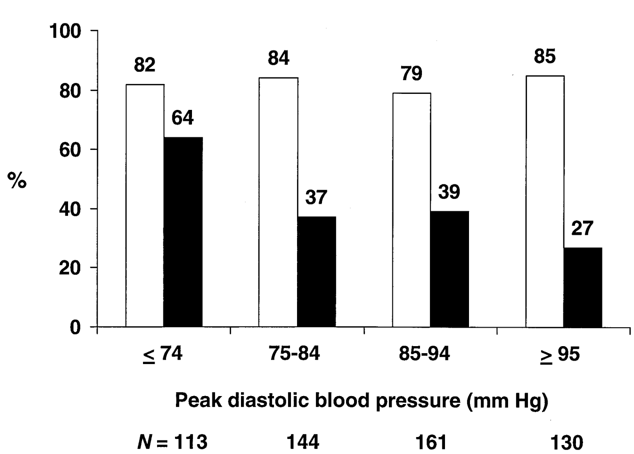

Figure 2. Sensitivity and specificity of exercise echocardiography according to peak diastolic blood pressure response to exercise. **Open bar** = sensitivity; **solid bar** = specificity.

DISCUSSION

This study demonstrated that a hypertensive response to exercise is associated with a greater likelihood of new or worsening abnormalities with exercise in the absence of angiographically significant coronary artery stenosis. False-positive results were twice as likely in patients with a hypertensive response to exercise. The likelihood of false-positive results increased with increasing SBPs and DBPs. Recognition of this phenomenon is important for interpreting individual exercise echocardiograms.

False-positive results of exercise echocardiography. Although the accuracy of exercise echocardiography has been verified in a large number of patients, false-positive results have been reported in a substantial number of studies (4,18). The understanding of the pathophysiology of a false-positive exercise echocardiographic result will be helpful not only in the interpretation of this noninvasive diagnostic test but also in the proper management of patients with suspected CAD. This information may be helpful in selecting appropriate patients for coronary angiography. One possible approach to evaluating patients with a positive echocardiographic result and hypertensive response to exercise may be to repeat the test after controlling blood pressure.

False-positive results may be associated with regional wall motion abnormalities, such as nonischemic cardiomyopathy. Bach et al. (19) reported that false-positive results of dobutamine stress echocardiography, defined as wall motion abnormalities predictive of CAD with <50% lumen stenosis on visual interpretation of coronary angiograms, occurred in 39 of 342 studies (11.4%). Potential sources for false-positive results may include poor endocardial visualization, normal heterogeneity in wall motion that is exaggerated during exercise, myocardial ischemia not associated with high-grade coronary stenoses and nonischemic cardiomyopathy. However, the influence of hypertensive response on results of stress echocardiography was not addressed.

Clinical implications of exercise-induced hypertension. Hypertension is often cited as a cause of false-positive exercise electrocardiographic results (7–10). In elderly and hypertensive subjects, the increase in systolic arterial pressure during exercise is frequently exaggerated even when blood pressure is well controlled at rest (20–22). An increase in arterial systolic pressure increases LV afterload and, thus, may reduce the extent of ejection. In a study of subjects referred for symptom-limited treadmill exercise testing and coronary angiography, hypertensive response to exercise predicted a lower prevalence of severe angiographic

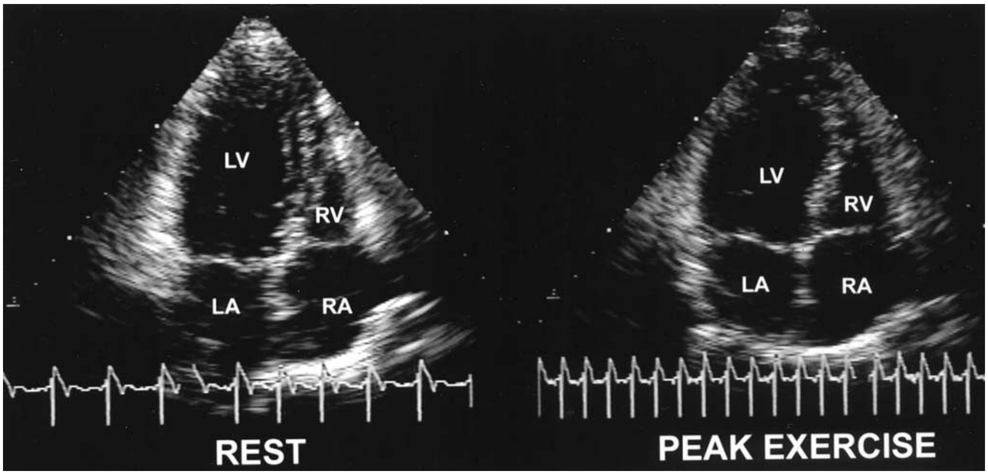

Figure 3. Exercise echocardiogram obtained from an apical four-chamber view of the heart in a 73-year-old woman with a hypertensive response to exercise. An end-systolic image taken immediately after peak exercise **(right)** shows an enlarged left ventricular (LV) cavity compared with image at rest **(left).** LA = left atrium; RA = right atrium; RV = right ventricle.

CAD and a lower adjusted mortality rate (23). In clinical practice, findings of severe global hypokinesis after exercise may lead to a presumptive diagnosis of left main or severe multivessel CAD but may occur in association with normal findings on coronary angiography in some patients with a hypertensive response. These clinical experiences prompted this clinical study.

Potential mechanisms of ischemia. Potential mechanisms by which a hypertensive response could cause abnormal wall motion may include an excessive rate-pressure product, which results in global subendocardial ischemia due to a mismatch between myocardial oxygen supply and demand. The potential for abnormal loading conditions to cause wall motion abnormalities is supported by the finding that healthy young adults can develop abnormal ventricular contractility by performing sudden vigorous exercise (24). An exaggerated SBP response has been proposed as a marker of LV hypertrophy (25). Previous investigations have shown that in healthy normotensive adults, hypertensive response to exercise may be associated with subsequent development of rest hypertension (15,26) and echocardiographic LV hypertrophy (14,27). Because of reduced coronary vasodilator reserve in patients with LV hypertrophy, global subendocardial ischemia may occur in hypertensive patients from abnormally elevated resistance at the coronary microvascular level.

Study limitations. When compared with findings in previous reports, the lower specificity of exercise echocardiography may be partly explained by test verification bias. Using exercise echocardiography to help in deciding whether to refer the patients to angiography modified the sensitivity and specificity of the test. Roger et al. (18) reported that in clinical practice test verification bias results in a lower specificity of exercise echocardiography.

Conclusions. In summary, new or worsening wall motion abnormalities may occur in patients without CAD who have a hypertensive response to exercise. The potential for false-positive results should be considered in the interpretation of these studies.

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